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Post-operative ventilation in lung transplant patients and correlation with outcomes: a retrospective study

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1. Introduction

The concept of ventilator induced lung injury (VILI) has been described more than 20 years ago (1,2). Lung injury can be the consequence of volotrauma when too high tidal volumes are delivered, to barotrauma when airway pressures are too high or to atelectrauma when some lungs area alternate between collapse and opening at every breath. Protective ventilation with low tidal volumes (VT) indexed to predicted body weight (PBW), moderately high plateau pressure and relatively high positive end-expiratory pressure (PEEP) has been recognized as effective in improving outcomes in patients suffering from acute respiratory distress syndrome (ARDS) (3).

The interest of delivering protective ventilation in other patients at risk for developing VILI has not been extensively described. Because transplanted lungs are exposed to cold ischemia after the retrieval process and then to ischemia-reperfusion injuries, they are probably particularly at risk for developing VILI. Protective ventilation strategies in the post-operative period should thus be of particular interest in lung transplanted patients. The effect of using such strategies after lung transplantation has however not been extensively described. In addition, there is some evidence that ventilation delivered in the post-operative period after lung transplantation is very heterogeneous and sometimes not very protective (4).

Primary graft dysfunction (PGD) is one of the most important cause of mortality and morbidity during the early post-transplantation period (0 to 30 days). In addition , PGD is correlated with an increased risk of developing a bronchiolitis obliterans syndrome, which is going to impact long term survival and quality of life (5).PGD usually occurs within the first 72 hours post-transplantation and affects nearly 30% of the transplanted patients (5). It is considered as the result of cold ischemia and reperfusion mechanisms resulting in pulmonary oedema, infiltrates and hypoxemia but could also be enhanced by non-protective ventilation (5, 6).

As according to the latest data of the International Society of Heart and Lung Transplantation (ISHLT), lung transplantation is widely performed around the world (7), the question of optimizing ventilatory support after lung transplantation is of major interest. In addition, it is important to be aware that even if the interest of applying lung protective ventilation strategies has been extensively described, recent studies have shown that the protective ventilation guidelines are often not optimally applied both in ARDS and in post-transplant patients (4, 8).

The main objective of this study was to analyse how mechanical ventilation was applied to the lung transplanted patients during their ICU stay in the Lausanne University Hospital ICU and to determine whether there were differences in the ventilation applied according to the lung disease that led to transplantation.

The second objective of this study was to assess whether the ventilation modalities applied in the post-operative period could be associated with lung transplant patients' outcomes, in particular with the ventilation duration and the ICU length of stay.

2. Methods

This study was a retrospective analysis. It took place in the Adult Intensive Care Unit (ICU) of the Lausanne University hospital (CHUV). Data were collected during the 16th of July 2014 to the 31st of October 2017 period.

2.1 Ethics committee

The study protocol was accepted by the Commission cantonale d'éthique de la recherche sur l'être humain (CER-VD) (protocole reference number 2017-01181). A waiver of consent was obtained for this retrospective study.

2.2 Inclusion/exclusion criteria

All the patients hospitalized during the study period in the ICU after bilateral lung transplantation were screened for inclusion in the study except if they had previously explicitly mentioned that they did not want to participate in a research project.

All the patients screened were included except if they had one of the following non-inclusion criterion: unilateral lung transplantation, concomitant transplantation of another organ, second lung transplantation or transplantation of lungs preconditioned using the ex vivo lung perfusion technique.

2.3 Data collection

Data were collected from the patients' medical file (Soarian and Archimede) and monitoring system (Metavision). The data were collected using an excel file. To minimise the risk of errors, we specified data limits for each excel file cell. The data collected are listed hereafter.

2.3.1 Patients characteristics and general data

Demographic and general patients' data were collected: age at the time of transplantation, sex, weight, height, reason for transplantation, whether or not the patient was on the emergency transplantation list (including the reason) and comorbidities (in particular past history of coronary or renal disease or diabetes). Predicted body weight (PBW) was calculated based on the patient's sex and height (9).

The dates of ICU admission and discharge, the date of hospital discharge, the destination after the hospital stay, the Simplified Acute Physiology Score (SAPS) II at ICU admission and the sequential organ failure assessment (SOFA) scores (10) at day 1 and 3 after transplantation were also recorded. In case of death in the ICU or during the hospital stay, the date and reason of death was also recorded.

The pulmonary graft dysfunction (PGD) score was computed at day 1 and 3. This score is a tool to determine the severity of acute lung injury after lung transplantation. Based on the presence/absence of pulmonary oedema on chest radiography and on ratio of arterial fraction of oxygen/fraction of inspired oxygen, ($Pa0_2/Fi0_2$), points are attributed from a total of 0 to 3 (11).

2.3.2 Invasive mechanical ventilation data.

The following general ventilation related data were collected during the ICU stay: interface for ventilation, date of extubation, total duration of mechanical ventilation, need for reintubation and need for tracheostomy.

In addition to these general ventilation data, the following parameters were collected every 6 hours from admission in the ICU to the 72^{sd} hour of ICU stay and then every 24h (censured at 60 days):

- Pulse oximetry, ventilation mode (volume controlled –VC-, pressure controlled –PC- or pressure support –PS-), inspired oxygen fraction
- Ventilator settings (according to the ventilation mode): set respiratory rate, inspiration/expiration ratio, set tidal volume or inspiratory pressure, set positive end expiratory pressure -PEEP-
- Monitored parameters (according to the ventilation mode): respiratory rate, tidal volume, peak pressure, plateau pressure, driving pressure for VC computed as plateau pressure – PEEP.

2.3.3 Non-invasive ventilatory support data

The following data were collected every 6 hours from admission in the ICU to the 72^{sd} hour of ICU stay and then every 24h (censured at 60 days):

- Use of non-invasive ventilation (NIV), total number of NIV sessions and total time spent under NIV, set inspiratory positive airway pressure (IPAP) and set PEEP.
- Use of high flow oxygen therapy, time in hours spent under high flow oxygen therapy, gaz flow and FIO_2 during high flow oxygen therapy

2.4 Data analysis

Descriptive statistics were performed in the global study population and in four subgroups separated according to the reason for transplantation (cystic fibrosis –CF-, chronic obstructive pulmonary disease –COPD-, interstitial lung disease –ILD- and other diseases). The normality of the data distribution was tested with the D'Agostino-Pearson test. As a majority of the variable had a non-normal distribution, the results are provided as median [IQR]. Comparisons between the subgroups were performed for continuous data according to the data distribution using one way ANOVA and multiple T-Tests with Dunn's correction for post-hoc pairwise comparisons or with the corresponding ANOVA on rank. Proportions were compared using a chi2 or Fisher exact test as appropriate.

To test the effect of non-protective ventilation with high VT, the patients were split in the two following groups: non-protective VT group when delivered VT were above 8ml/kg PBW during more than 25% of time and protective VT group when delivered VT were lower than 8ml/kg PBW during more than 75% of time. Patients' characteristics and outcomes were compared between the two groups using T-test or Mann-Whitney tests according to the data distribution.

To test the effect of non-protective ventilation with high driving pressures (DP), defined as plateau pressure - PEEP, the patients ventilated in volume assist control (VAC) were split in the two following groups: non-protective DP group when DP was higher than 15 cmH_2O during more than 25% of time and protective DP group when DP was lower than 15 cmH_2O during more than 75% of time. Patients' characteristics and outcomes were compared between the two groups using T-test or Mann-Whitney tests according to the data distribution.

3. Results

3.1 Patients characteristics

Sixty-seven patients received lung transplant in the Lausanne University Hospital during the 16.07.2014 to 31.10.2017 period. Seven patients were excluded from the present analysis, one because of unavailability of his medical record and 6 because they had one of the predefined exclusion criterion (second lung transplant or concomitant transplant of another organ). No unilateral lung transplants were performed during the study period.

Sixty patients were consequently included in the present analysis. The main reason for transplantation was cystic fibrosis (16/60 patients; 27%) followed by chronic obstructive lung disease (COPD) (15/60 patients; 25%), interstitial lung disease (ILD) (15/60 patient; 25%) and other diseases (14/60; 23%). Details are shown in Figure 1.

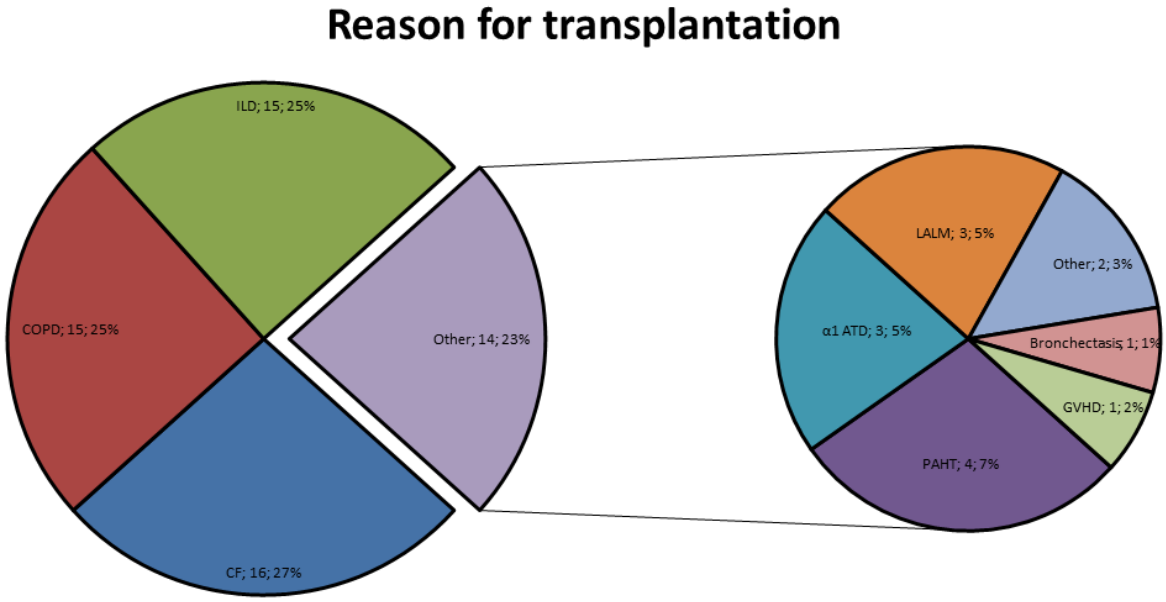


Figure 1 : Reasons for transplantation by disease category and number of patients with the disease (n(%)).
CF = cystic fibrosis ; COPD = chronic obstructive pulmonary disease ; IPF = idiopathic pulmonary fibrosis ; PF = pulmonary fibrosis ; CTD = connective tissue disease ; LALM = leiangioleiomyomatosis ; GVHD = graft versus host disease ; PAHT = pulmonary arterial hypertension ; α1 ATD = α1 antitrypsin deficiency

Among the 60 patients included, 6 of them were transplanted in emergency. The reasons for emergency were intubation because of acute respiratory failure (4/6 (66%)) and severe pulmonary arterial hypertension related hemodynamic instability (2/6 (33%)). The repartition of the patients transplanted in emergency according to the reason for transplantation is mentioned in Figure 2.

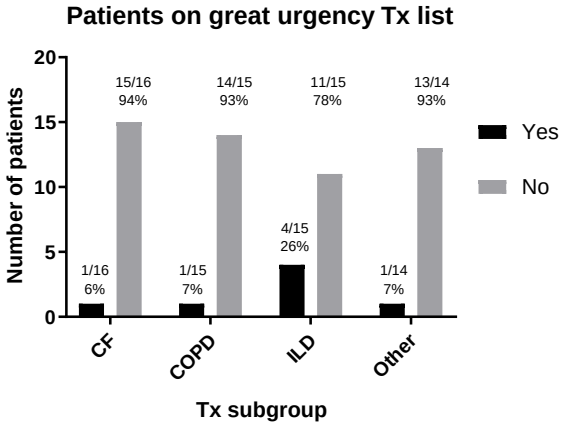


Figure 2 : Patients transplanted in emergency according to the reason for transplantation. Numbers and percentages.
CF = cystic fibrosis COPD = chronic obstructive lung disease ILD = interstitial lung disease Tx = transplantation

Among the 60 included patients, twenty-nine of them were males (48%) and 31 females (52%). At the time of transplantation, median age was 48.0 years [32.8-59.0], median height was 168 cm [159-174], median weight was 60 kg [52-71], and median BMI was 22.2 kg/m^2 [19.1-24.4]. The highest BMI value was 33.3 kg/m^2.Concerning the comorbidities at the time of transplantation, only two patients were known for chronic coronary disease (3%) and 6 suffered from diabetes (6%). No patient was known for chronic renal failure.

General patients' characteristics for the subgroups of patients according to the reason for transplantation are given in Table 1.

General characteristics	CF	COPD	ILD	Other reason for transplantation	All	ANOVAs
Age (y)	28±10 [b) c)]	59±5 [a)d)]	52±11 [a),]	43±12 [b)]	46±14	<0.0001
Height (cm)	167±10	165±8	170±10	165±9	167±9	Ns
Weight (kg)	54.3±11.8 [c)]	61.6±11.1	73.4±15 [a)]	62.7±15.5	63 ± 15.0	<0.0001
Predicted body weight	61±11.2	59.1±8.9	63.9±11	58.1±10.2	61 ±10	Ns

Men	8 (50%)	7 (47%)	9 (60%)	5 (36%)	29 (48%)	Ns
Women	8 (50%)	8 (53%)	6 (40%)	9 (64%)	31 (52%)	Ns
Coronary arteries disease	0	2 (13%)	0	0	2 (3%)	Ns
Chronic renal disease	0	0	0	0	0	Ns
Diabetes	6 (37%)	0	0	0	6 (10%)	Ns

Table 1 : General characteristics according to the reason for transplantation and for all the patients (n=60). a) p-value < 0.05 compared to CF, b) p-value < 0.05 compared to COPD, c) p-value < 0.05 compared to ILD ,d) p-value < 0.05 compared to Other
CF = cystic fibrosis COPD = chronic obstructive lung disease ILD = interstitial lung disease Other = other patients

3.2 Gravity scores

Overall, SAPS II score at admission was 32 [27-37] corresponding to a predicted mortality of 14.7 % [7.9-23.6]. SOFA score at day 1 was 5 [4-7]. PGD scores at day 1 and 3 are mentioned in table 2. SAPS II, SOFA score and PGD score for the subgroups of patients according to the reason for transplantation are mentioned in Table 2 and Figure 3.

Score	CF	COPD	ILD	Other	All	ANOVAs
SAPS II	27 [23-35]	34 [30-37]	32 [27.38]	35 [26-43]	32 [27.37]	Ns
SOFA day 1	5 [3-5] [c][d]	5 [3.2-7]	7 [5.2-9][a]	8 [5.5-10][a]	5 [4-7]	0.0056
SOFA day 3	2 [1.5-4]	4 [2-6]	10.5 [4.2-13.7]	5.5 [2.5-10.5]	3.5 [2-7.25]	Ns
PGD 0-1 day 1	11/16	9/15	5/15	5/14	30	Ns
PGD 0-1 day 3	12/16	9/15	6/15	10/14	30	Ns
PGD > 1 day 1	5/16	6/15	10/15	9/14	20	Ns
PGD > 1 day 3	4/16	6/15	9/15	4/14	23	Ns

Table 2 : Gravity Score data according to subgroups of reason for transplantation and for all the patients (n=60). a) p-value < 0.05 compared to CF, b) p-value < 0.05 compared to COPD, c) p-value < 0.05 compared to ILD ,d) p-value < 0.05 compared to Other.
CF = cystic fibrosis COPD = chronic obstructive lung disease ILD = interstitial lung disease Other = other patients. PGD = primary graft dysfunction SOFA : sequential organ failure assessment SAPS = simplified acute physiology score

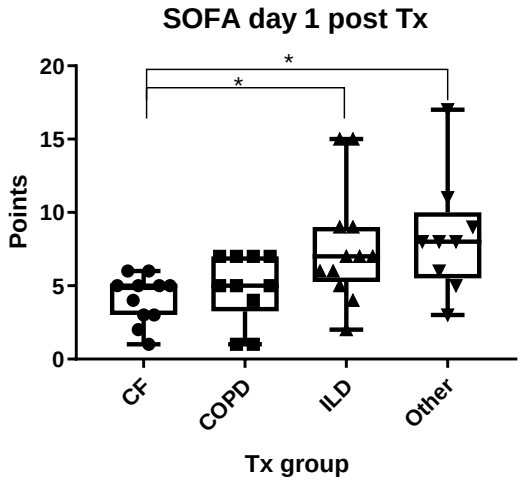


Figure 3 : SOFA score at day 1 post transplantation according to the reason for transplantation.
CF = cystic fibrosis COPD = chronic obstructive lung disease ILD = interstitial lung disease Tx = transplantation

3.3 General outcomes

Overall, the lung transplanted patients stayed in the hospital (including stay in ICU) for a median of 18.8 [14.0-29.6] days. They stayed in the ICU for a median of 4.7 days [3.1-9.6]. General outcome data for the subgroups of patients according to the reason for transplantation are given in Table 3.

Outcomes	CF	COPD	ILD	Other	All	ANOVAs
Stay in ICU (days)	4.5 [3.7-7.8]	4.1 [2.5-7.6]	8.9 [4.3-25.9]	5.3 [11-17]	4.7 [3.1-9.6]	Ns
Total stay in hospital (days)	20.5 [16.5-27.5]	17.7 [13.9-20.4]	18.3 [10.6-41.9]	26.9 [11.8-45]	18.8 [14-29.6]	Ns

Table 3 : General outcome according to subgroups of reason for transplantation and for all the patients (n=60). a) p-value < 0.05 compared to CF, b) p-value < 0.05 compared to COPD, c) p-value < 0.05 compared to ILD ,d) p-value < 0.05 compared to Other
CF = cystic fibrosis COPD = chronic obstructive lung disease ILD = interstitial lung disease Other = other patients

Two patients died during the hospital stay. These two patients died in the ICU respectively 67 days after transplantation in a context of persistent respiratory failure with very difficult weaning and 68 days because of refractory septic shock of abdominal origin.

Thirty one patients (52%) were discharged to another hospital (including rehabilitation centres). The others 29 (48 %) patients were discharged home.

3.4 Ventilation data

3.4.1 Interface used, ventilation duration and information related to weaning from mechanical ventilation

All patients were mechanically ventilated through an endotracheal tube at ICU admission. Median duration of invasive mechanical ventilation was 1.0 [0.6-3.6] day. Extreme durations of invasive mechanical ventilation were 4 hours 7 minutes and 67 days. Twenty one patients (35%) were mechanically ventilated during more than 48h. Ten of them (17% of total) were ventilated during more than 7 days. Overall, 5 over 60 patients had to be reintubated. The number of reintubated patients per subgroups is given in Table 4.

Mechanical ventilation duration and need for reintubation in the subgroups according to the reason for transplantation are illustrated in Figure 4 and Table 4.

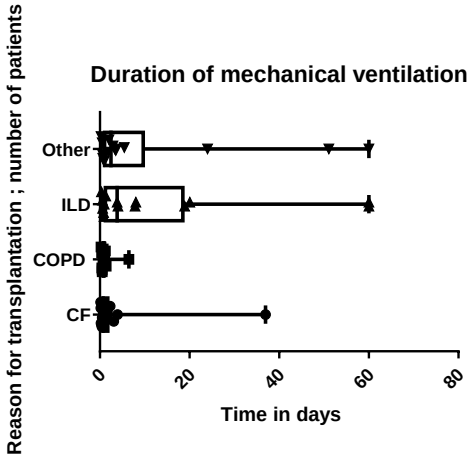
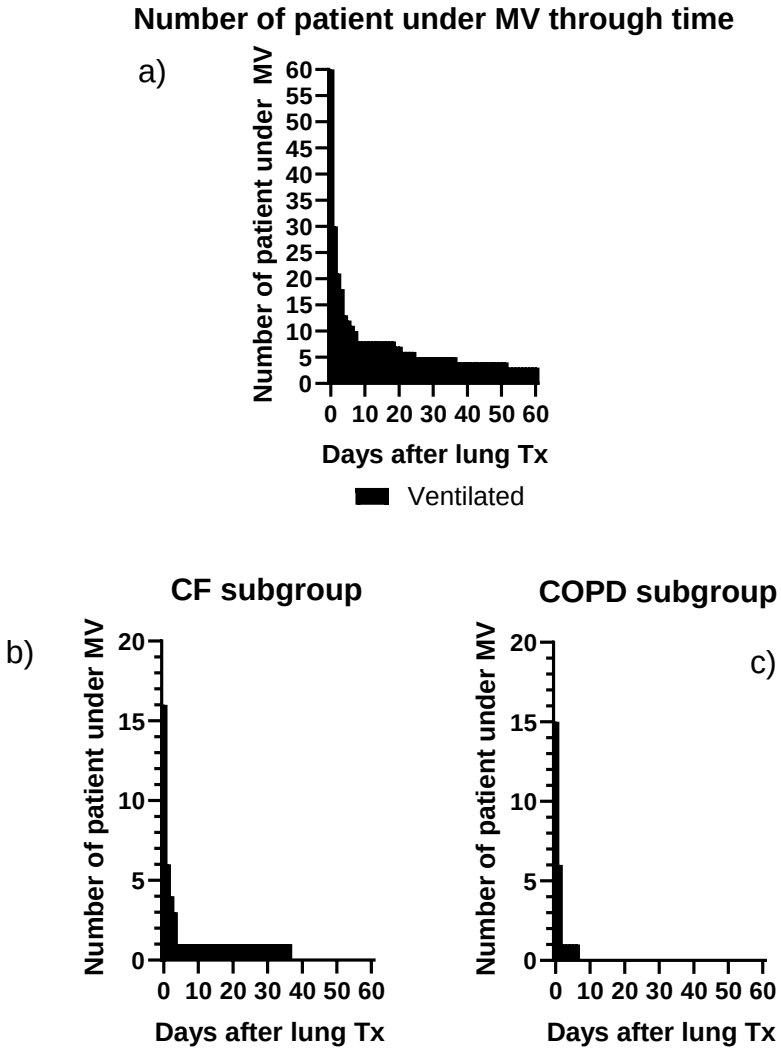


Figure 4: Duration of mechanical ventilation in days according to the subgroups of main reason for transplantation.
CF = cystic fibrosis COPD = chronic obstructive lung disease ILD = interstitial lung disease.

Ventilation outcome	CF group	COPD group	ILD group	Other group	All	ANOVAs
Duration of MV	0.7 [c)d)] [0.4-2.1]	0.7 [c)d)] [0.5-1.2]	3.86 [a)b)] [0.81-18.9]	2.4 [a)b)] [0.63-10]	1 [0.6-3.6]	0.0254
MV more than 48h	4/16 (25%)	1/15 (7%)	8/15 (53%)	7/14 (50%)	20/60 (33%)	0.0237
MV more than 7 days	1/16 (6%)	0/15	6/15 (40%)	3/14 (21%)	10/60 (16%)	0.0158
Reintubation	1/16 (6%)	1/15 (7%)	3/15 (20%)	0/14 (0%)	5/60 (8%)	Ns

Table 4 : Ventilation outcome data according to subgroups of reason for transplantation and for all the patients (n=60). a) p-value < 0.05 compared to CF, b) p-value < 0.05 compared to COPD, c) p-value < 0.05 compared to ILD ,d) p-value < 0.05 compared to Other
CF = cystic fibrosis COPD = chronic obstructive lung disease ILD = interstitial lung disease Other = other patients MV = mechanical ventilation

Figure 5 represents the total number of patients under invasive mechanical ventilation over time both for all the patients and for the subgroups of patients according to the reason for transplantation.



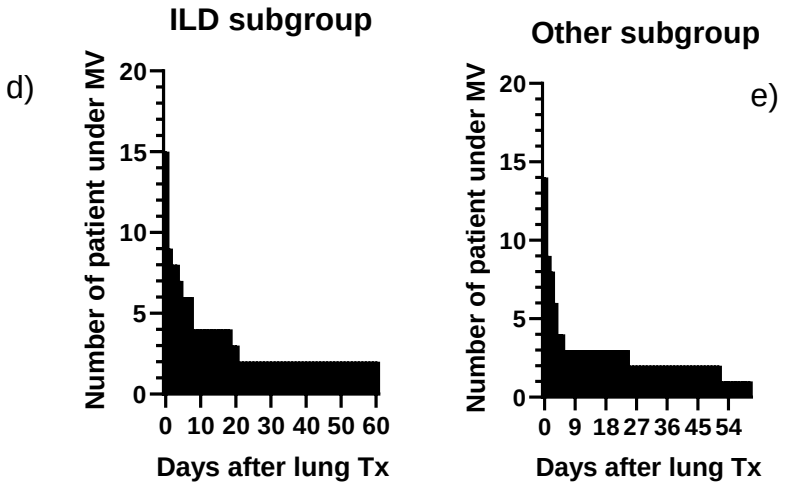


Figure 5 : Number of patients under invasive mechanical ventilation over time for all the patients (a) and according to the reason for transplantation (b for CF group, c for COPD group, d for ILD group, e for other patients).
CF =cystic fibrosis COPD = chronic obstructive lung disease ILD = interstitial lung disease Other = other patients MV = mechanical ventilation Tx = transplantation

Nine patients (15%) were tracheotomized during the ICU stay. One of them suffered from CF, 1 from COPD, 4 from ILD and 3 from other disease (p ANOVA >0.05)

3.4.2 Ventilatory modes and ventilator parameters

For controlled ventilation, volume assist control (VAC) mode was used in 57 (95%) patients. Pressure assist control (PAC) was used in 13 (22%) patients. The use of these two modes is not mutually exclusive.

Pressure support ventilation (PSV) was used for weaning in all the patients. In 34 (57%) patients, PSV was used during more than 6 hours. Total duration spent under PSV, computed as the total number of 6-hour periods spent under PSV, was in median 1 [0-4] periods. For CF, COPD, ILD and other patients this duration was respectively 0 [0-1], 0 [0-2], 6 [1-43], 2.5 [0-4] (p ANOVA = 0.0069, CF group was different from ILD group and COPD group was different from ILD group with p-value <0.05).

Detailed set and measured ventilator parameters are given for the global population and for the subgroups in Table 5 for all modes, controlled modes, volume assist control, pressure assist control and pressure support modes

All modes						
Parameter	**CF**	**COPD**	**ILD**	**Other**	**All**	**ANOVAs**
F_iO_2, all stay	29 [2-35] [c)d)]	29 [24-35.3] [c)d)]	35 [28-43] [b)]	31 [28-40] [a)b)]	35 [30-41]	<0.0001
PEEP during MV	6 [5-8] [b)]	5 [5-6] [a)c)]	6 [5-8] [b)]	6 [5-8]	6[5-8]	0.0193
All controlled modes						
Set parameter	**CF**	**COPD**	**ILD**	**Other**	**All**	**ANOVAs**
Respiratory rate [breath/min]	20 [17-23] [c)d)]	18 [16-20] [c)]	15 [14-18] [a)b)d)]	17 [16-20] [a)c)]	17 [15-20]	<0.0001
Volume assist control						
Set parameters	**CF**	**COPD**	**ILD**	**Other**	**All**	**ANOVAs**
VT [ml]	359 [339-448]	400 [350-445]	400 [310-450]	400 [352-450]	400 [340-450]	Ns
VT per PBW [ml/kg]	6.0 [5.7-6.6] [b)]	6.8 [6.5-7.2] [a)c)d)]	6.1 [5.9-6.9] [b)]	6.2 [5.8-6.8] [b)]	6.2 [5.7-6.8]	<0.0001
PEEP [cmH_20]	7.7 [6-8] [b)]	5 [5-6] [a)c)d)]	7 [5-8] [b)]	6.5 [5-8] [b)]	7 [5-8]	<0.0001
Measured parameters	**CF**	**COPD**	**ILD**	**Other**	**All**	**ANOVAs**
P peak	29 [24-34] [b)d)]	24 [21-26] [a)c)d)]	27 [23-31] [b)]	26 [23.5-29] [a)b)]	26 [23-31]	<0.0001
P plat	23 [19-28] [b)]	19 [16-20] [a)c)d)]	23 [20-26] [b)]	21 [19.25-25] [b)]	21 [19-26]	<0.0001
Driving pressure	15 [13-20] [b)]	13 [11-14] [a)c)d)]	16 [14-18] [b)]	15 [14-17] [b)]	15 [13-18]	<0.0001
Pressure assist control						
Set parameter	**CF**	**COPD**	**ILD**	**Other**	**All**	**ANOVAs**
P insp	13 [13-17]	14 [13-15]	17 [16-18]	15[15-20]	16 [13-19]	Ns
Measured parameter	**CF**	**COPD**	**ILD**	**Other**	**All**	**ANOVAs**
VT[[ml]	410 [297-508]	466 [375-517]	388 [308-475]	230 [164-420]	387 [226-459]	0.0217
Pressure support						
Set parameter	**CF**	**COPD**	**ILD**	**Other**	**All**	**ANOVAs**
Pressure support level	10 [8-20] [c)d)]	8 [7-18] [d)]	13 [12-24] [a)d)]	13 [12-22] [a)b)c)]	13 [10-24]	<0.0001
Measured parameter	**CF**	**COPD**	**ILD**	**Other**	**All**	**ANOVAs**
VT [ml]	360 [290-437] [b)]	467 [372-679] [a)c)d)]	403 [309-501] [b)]	358 [287-416] [b)]	377 [302-471]	0.0002

Table 5 : Ventilation parameters, sorted by mode of mechanical ventilation for all the patients [n=60] and according to the reason for transplantation. a] p-value < 0.05 compared to CF, b] p-value < 0.05 compared to COPD, c] p-value < 0.05 compared to ILD ,d] p-value < 0.05 compared to Other.
CF = cystic fibrosis COPD = chronic obstructive lung disease ILD = interstitial lung disease Other = other disease, F_iO_2 = inspired oxygen fraction, volume PEEP = positive end expiratory pressure, MV = mechanical ventilation, VT = tidal volume; PBW =predicted body weight Ppeak = peak pressure, P plat= plateau pressure, P insp = inspiratory pressure

The major determinants characterising protective ventilation during volume assist control ventilation are mentioned in Table 6.

Volume assist control						
Set parameters	**CF**	**COPD**	**ILD**	**Other**	**All**	**ANOVAs**
VT < 6ml/kg in %	0 [0-3]	0 [0-0]	10 [0-53]	0 [0-5]	0 [0-50]	Ns
6 < VT <8 ml/kg in %	2 [0-2]	100 [67-100]	76 [45-100]	100 [17-100]	89 [24-100]	Ns
PEEP <8 cmH_20 in %	100 [85-100]	100 [100-100]	100 [60-100]	100 [83-100]	100 [100-100]	Ns
PEEP <6 cmH_20 in %	33 [0-100]	100 [100-100][c)]	20 [0-95][b)]	51 [0-100]	100 [50-100]	0.0271
Mesured parameters	**CF**	**COPD**	**ILD**	**Other**	**All**	**ANOVAs**
P plat <30 cmH_20 in %	100 [100-100]	100 [100-100]	100 [95-100]	100 [100-100]	100 [100-100]	Ns
P plat <25 cmH_20 in %	100 [84-100]	100 [100-100][c)]	86 [62-100][b)]	100 [94-100]	100 [86-100]	0.0183
P plat <20 cmH_20 in %	45 [0-92]	100 [63-100]	38 [0-58]	53 [25-100]	56 [21-100]	Ns
Driving pressure <15 cmH_20 in %	100 [65.9-100]	100 [83-100]	50 [33-100]	64.70 [46-100]	83.76 [49-100]	Ns

Table 6 : Determinants of protective ventilation in volume assist control for all the patients (n=60) and according to the reason for transplantation. Total percentages of recorded values. a) p-value < 0.05 compared to CF, b) p-value < 0.05 compared to COPD, c) p-value < 0.05 compared to ILD ,d) p-value < 0.05 compared to Other.
CF = cystic fibrosis COPD = chronic obstructive lung disease ILD = interstitial lung disease Other = other disease; VT = tidal volume PEEP = positive end expiratory pressure; Pplat = Plateau pressure

3.4.3 Non-invasive ventilatory support

Among the 60 patients and during their ICU stay, 39 received non-invasive ventilation (65%), for a median number of sessions of 9 [5-12] and for a median duration of 6.9 hours [3.1-10]. Median inspiratory positive airway pressure (IPAP) was set at 13 [10-24] cmH_20 and median PEEP at 7 cmH_2O [6-8].

High flow oxygen therapy was used for 8 patients (13%) for a median of 37.1 [11.6-99.7] hours and with a median gas flow of 35 [32.5-47.5] l/min.

Data sorted by patients' subgroups are displayed in Table 7.

NIV	Parameter	CF	COPD	ILD	Other	All	ANOVAs
NIV	Number of sessions	2.5 [0-7.3]	5 [0-10.5]	9 [1.5-16.5]	1 [0-6.8]	9 [5-12]	Ns
NIV	Hours under NIV	3.2 [0-7.7]	3.7 [0-7.9]	6.5 [0.4-9.6]	1.1 [0-5.7]	6.9 [31-10]	Ns
NIV	IPAP	12 [10-13]	13 [11-15]	13 [12-15]	12 [10.75-14]	13 [11-14]	Ns
NIV	PEEP	7 [5-7][c)]	7 [6-7.5][c)]	7 [7-8][a)b)]	7 [6-7]	7 [6-8]	0.0012
HFOT	Oxygen flow HD	No values	30 [30-32.5]	No values	No values	35 [32. -47.5]	-

Table 7: non-invasive ventilator support results according to subgroups of reason for transplantation and for all the patients (n=60). a) p-value < 0.05 compared to CF, b) p-value < 0.05 compared to COPD, c) p-value < 0.05 compared to ILD ,d) p-value < 0.05 compared to Other.
CF = cystic fibrosis COPD = chronic obstructive lung disease ILD = interstitial lung disease Other = other patients NIV = non-invasive ventilation HFOT = high flow oxygen therapy IPAP = inspiratory positive airway pressure

3.5 Patients characteristics and outcomes according to the predefined protective and non-protective VT groups

3.5.1 Patients characteristics

Among the 57 patients ventilated in VAC, 47 (82.5 %) were ventilated with set VT of less than 8 ml/kg PBW for more than 75 % of time (Protective VT group). The 10 remaining patients were ventilated with set tidal volumes of more than 8ml/kg PBW for more than 25% of time (Non-protective VT group). In the protective VT group, median VT/kg PBW was 6.1 [5.7-6.7] ml/kg. In the non-protective VT group, median VT/kg PBW was 7.9 [6.5-8.7]. Difference in VT/kg was significant between both groups ($p < 0.0001$).

General patients' characteristics in the protective and non-protective VT groups are given in Table 8.

General data	Protective VT N = 47	Non-Protective VT N = 10	P value
Age [y]	50 [33-59]	35 [24-61]	ns
Height [cm]	170 [163-175]	155 [151-160]	<0.0001
Weight [kg]	60 [52-75]	55 [49-64]	ns
Predicted body weight	65.9 [55.1-70.5]	47.8 [44.7-52.8]	<0.0001
Men/Women	27/20	1/9	0.0119
On emergency list	6/47 (12,8%)	1/10 (10%)	Ns

Table 8 : Patients characteristics according to subgroups of tidal volumes. *Vt = tidal volume*

3.5.2 Gravity score

SAPS II score was in median 32 [27-38] for the protective VT group and 34 [24.5-39.5] for the non-protective VT group (p >0.05). SOFA and PGD scores for the protective and non-protective VT groups are given in Table 9.

Score	Protective VT N = 47	Non-Protective VT N = 10	ANOVAs
SOFA day 1	7 [6-9]	7 [4-7.7]	Ns
SOFA day 3	5.5 [3.2-8.7]	1.5 [1-11.7]	Ns
PGD 0-1 day 1	25/47	5/10	Ns
PGD 0-1 day 3	20/47	6/10	Ns
PGD > 1 day 1	22/47	5/10	Ns
PGD > 1 day 3	27/47	4/10	Ns

Table 9: SOFA and PGD scores according to subgroups of tidal volume. *Vt = tidal volume SOFA = sequential organ failure assessment PGD = primary graft dysfunction*

3.5.3 General outcome

General outcome data for the protective and non-protective VT groups are given in Table 10.

Outcomes	Protective VT N = 47	Non-Protective VT N = 10	P value
Stay in ICU (days)	4.8 [2.9-9.9]	5 [5.4-19.7]	Ns
Total stay in hospital (days)	18.7 [15.9-30]	20.7 [12.7-37.8]	Ns

Table 10 : Outcomes according to the protective and non-protective VT groups. *Vt = tidal volume*

3.5.5 Ventilation duration and information related to weaning from mechanical ventilation

Detailed ventilation duration for the protective and non-protective VT groups are given in Table 11

Ventilation outcome	Protective VT N = 47	Non-Protective VT N = 10	P values
Duration of MV (days)	1 [0.5-3.9]	0.9 [0.5-6]	Ns
MV more than 48h	19/47	2/10	Ns
MV more than 7 days	8/47	2/10	Ns
Reintubation	4/47	1/10	Ns

Table 11 : ventilation outcomes for the protective and non-protective VT groups. *Vt = tidal volume MV = mechanical ventilation*

Figure 6 represents the total number of patients under invasive mechanical ventilation over time according to the groups of tidal volume (protective or non-protective VT groups).

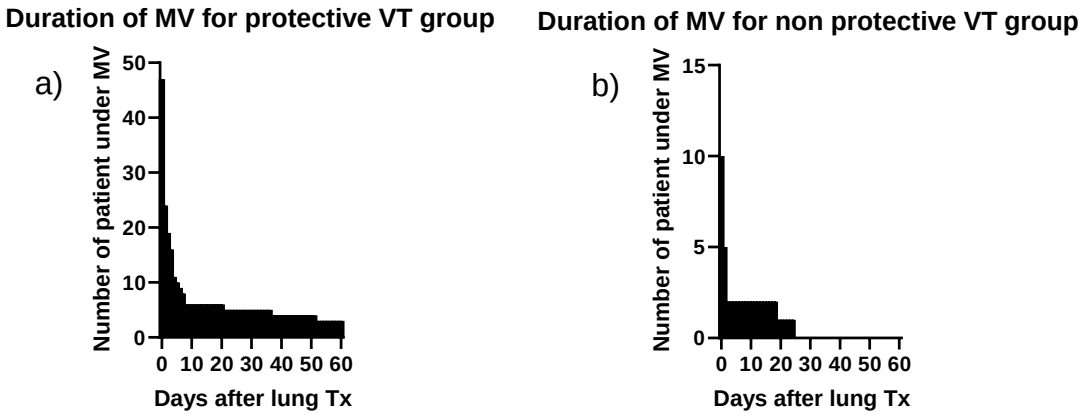


Figure 6 : Number of patients under mechanical ventilation over time. A) for the protective VT group B) for the non-protective VT group.
MV= mechanical ventilation VT= tidal volume Tx = transplantation

Six patients (12.8%) from the protective VT group had to be tracheotomised. For the other group, 3 patients (30%) required tracheotomy (p >0.05).

Concerning weaning from mechanical ventilation, the total PSV duration given as 6-hour periods under PSV was in median 4 [1.5-50] for the protective VT group and 2 [1-55] for the non-protective VT group (p >0.05).

For the protective VT group, NIV was used in 29/47 patients (62%). For the non-protective VT group, it was used in 8/10 patients (80%) (p >0.05).

3.6 Patients characteristics and outcomes according to the predefined protective and non-protective driving pressure (DP) groups

Among the 57 patients ventilated in VAC, 34 (59.6 %) were ventilated with DP of less than 15 cmH_2O for more than 75 % of time (Protective DP group). The 23 remaining patients were ventilated with DP of more than 15 cmH_2O for more than 25% of time (Non-protective DP group). In the protective DP group, median DP was 13 [11-15],

whereas non protective DP group has in median a DP value of 17 [15-20] (p<0.0001).

3.6.1 Patients characteristics

General patients' characteristics in the protective and non-protective DP groups are given in Table 12.

General data	Protective DP	Non protective DP	P value
Age [y]	54 [29-60]	48 [33-59]	Ns
Height [cm]	170 [158-175]	166 [158-173]	Ns
Weight [kg]	58 [51-70]	66 [52-78]	Ns
Predicted body weight	64 [51-70]	60 [50-69]	Ns
Men	19	10	Ns
Women	15	13	
On emergency list	6/47	1/10	Ns

Table 12 : ventilation outcomes according to subgroups of driving pressure. *DP = driving pressure y = years cm =centimeters kg =kilogram*

3.6.2 Gravity score

SAPS II score was in median 30 [26-35] for the protective DP group and 37 [29-46] for the non-protective DP group (p =0.0039).SOFA score at day 1 is displayed in figure 7.

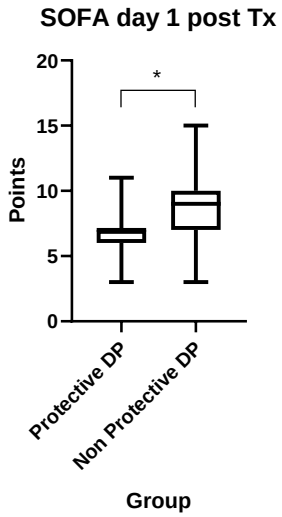


Figure 7 : SOFA score at day 1 post lung transplant was in median 7 [6-7] in DP < 15 group and 9 [7-10] in DP > 15 group, with a p-value of 0.0032.
DP = driving pressure Tx = transplantation SOFA = sequential organ failure assessment

SOFA score at day 3 was 3.5 [1.7-5.5] in the protective DP group and 8 [3-13.5] in the non-protective DP group (p>0.05). PGD scores for both groups are given in table 13.

PGD Score	Protective DP	Non protective DP	P value
PGD 0-1 day 1	21 (61.8%)	9 (39.1%)	Ns
PGD 2-3 day 1	13 (38.2%)	14 (60.9%)	
PGD 0-1 day 3	25 (73.5%)	9 (39.1%)	0.0136
PGD 2-3 day 3	9 (26.5%)	14 (60.9%)	

Table 13 : PGD scores according to subgroups of driving pressure. *DP = driving pressure PGD = primary graft dysfunction*

3.6.3 General outcome

Stay duration in the ICU in days was in median 4.2 [2.8-6.5] days for the protective DP group, and 13.6 [4.2-32.8] days for the non-protective DP group (p =0.0005), as shown in figure 8.

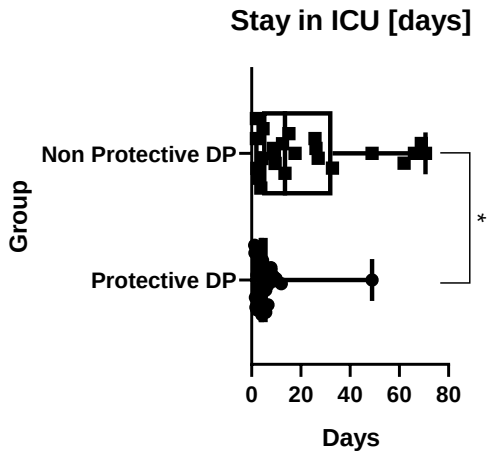


Figure 8 : duration of stay in ICU after lung transplantation, according to the groups of DP
DP = driving pressure. ICU = intensive care unit

Total stay in hospital was 18.8 [16.3-23] days in the protective DP group whereas it was 29.4 [11.9-49] days in the non-protective DP group (p>0.05).

The two patients who died during the hospital stay belong to the non-protective DP group.

3.6.4 Ventilation duration and information related to weaning from mechanical ventilation

Protective DP group had a median duration of mechanical ventilation of 0.7 [0.5-1.5] days. In non-protective DP group, median duration of MV was 4 [0.7-24] days (p-value 0.0002). This is illustrated in figure 9.

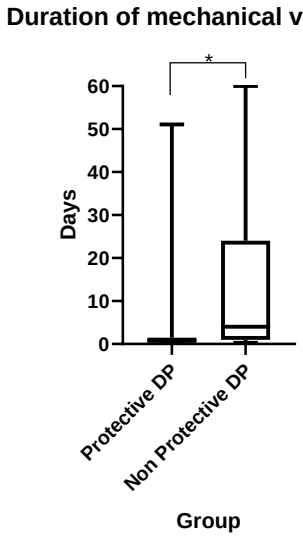


Figure 9 : Duration of mechanical ventilation according to the protective and non-protective DP. DP = driving pressure

Figure 10 shows the number of patients under mechanical ventilation over time according to the protective and non-protective DP groups

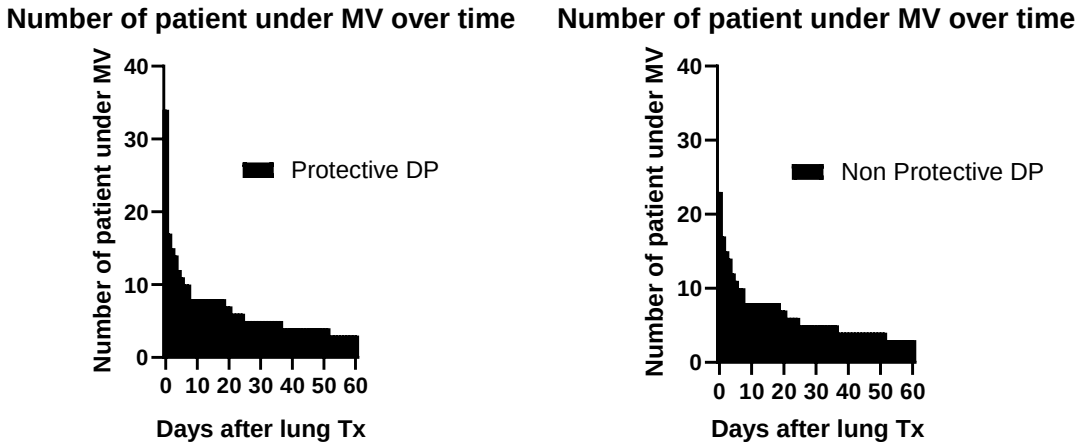


Figure 10: mechanical ventilation over time for a) protective DP group and b) non protective DP
DP = driving pressure

Patients from the non-protective DP group were more likely to be ventilated more than 48h (OR 7 [2-23], p = 0.001) and more than 7 days (OR 25 [3-282], p = 0.0002) than patients from the protective DP group, as shown in figure 11.

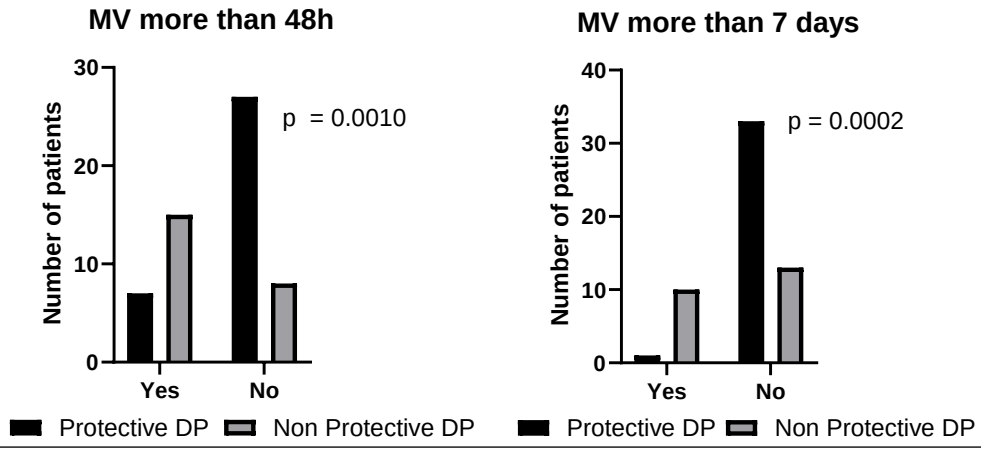


Figure 11 : duration of mechanical ventilation for more than 48h (a) or more than 7 days (b) according to the groups of driving pressure. *DP = driving pressure. MV = mechanical ventilation*

Reintubation occurred in 2 of 34 patients (5.9%) in the protective DP group, and in 3/23 (13.0%) in the non-protective DP group (p>0.05). Two patients of 34 (5.9%) underwent tracheotomy in the DP group, and 8/23 (34.8%) in the non-protective DP group (p=0.0105).

4. Discussion

We have analysed 60 patients who were lung transplanted in the Lausanne University hospital during the 16.07.2014 to 31.10.2017 period. Among these patients, the main reason for transplantation was cystic fibrosis (16/60 patients; 27%) followed by COPD (15/60 patients; 25%), Interstitial lung disease (ILD) (15/60 patient; 25%) and others included patients (14/60; 23). These findings are similar to the latest statistics of adult lung transplantation worldwide according to the ISHLT (7)

Six patients were transplanted while on an emergency transplantation list. Four of them suffered from ILD. We can hypothesize that this is due to the fact that the natural history of ILD is often characterized by sudden and irreversible exacerbations leading to acute respiratory failure and need for mechanical ventilation. In addition, ILD patients often suffer from systemic disease (12,13).

As expected, the baseline patients' characteristics were not the same according to the reason for transplantation. The CF patients were younger than the other subgroups whereas the COPD patients were the oldest. Interestingly, height was not different but weight was higher in ILD patients compared to CF patients.

The severity at admission expressed by the SAPS II score was similar for the different pathologies leading to transplantation. Oppositely, at day 1, the SOFA score was lower in CF patients compared to ILD and other disease patients. In the early post-operative period, ILD and other disease patients were thus more severely ill.

We could hypothesize that because ILD patients more often have a systemic disease, they could be more at risk of developing organ failure in the early post-operative period. Interestingly, ILD and other disease patients had not higher PGD score at day 1 and 3 post graft compared to CF and COPD patients.

As they were more severely ill at day 1 after transplantation, we could expect worse outcome in ILD and other disease patients. In line, even if it was not significant, ILD and other patients tended to stay longer in the ICU than the patients of the other groups. ILD patients however did not stay longer in the hospital. Interestingly, no COPD patients stayed in the ICU for a prolonged period of time. Oppositely 1 CF patient, 5 ILD patients and 3 other disease patients stayed in the ICU for a long period of time. As there seems to be a trend for a prolonged stay among the ILD and other disease group, we could hypothesize that if we had included a higher number of patients this difference could have become significant.

Concerning the general patient's outcome, it is interesting to underline that overall hospital mortality was very low. Only two patients died during their hospital stay.

If we now consider the ventilatory support delivered to the transplanted patients, all the patients were ventilated through an endotracheal tube at ICU admission. The median duration of mechanical ventilation was very low (1.0 [0.6-3.6] day). This finding is concordant with a recent international survey concerning mechanical ventilation after lung transplantation (4).Median ventilation duration was 0.6 days in the CF and COPD groups. Duration of ventilation was much longer in the ILD and other disease groups. The mechanical ventilation duration was similar in these last two groups. Except one CF patients, all the patients who were ventilated more than 7 days were ILD and other disease patients. This again underlines that these patients are the most severely ill. In line, the majority of patients who had to be tracheostomized were ILD and other disease patients. This may indicate that ILD and other disease patients were more prone to have a difficult mechanical ventilation weaning.

Concerning mechanical ventilation settings, it is important to underline that the large majority of delivered tidal volumes were of less than 8 ml/kg PBW and thus is the recommended range (14). Our data showed that delivered tidal volumes indexed for PBW during VAC ventilation was higher in COPD patients. The first potential explanation for the use of higher tidal volumes in the post transplantation period in COPD patients is that previously hypercapnic patients keep abnormal respiratory drive regulation (15) responsible for persistent hypercapnia during several days after transplantation. To try to correct blood gas analyses the caregivers could tend to use higher tidal volumes. This could also however be explained by the fact that the caregivers are used to ventilate COPD patients with higher tidal volumes as they are supposed to have higher vital capacity and/or higher pulmonary compliance. Of course this is no more the case after lung transplantation but we could imagine that the caregivers do not systematically take this into account.

Interestingly, independently from the reason for transplantation, patients who received more often VT > 8ml/kg were smaller and had a higher body mass index. This suggests that small and overweighed patients are more at risk of receiving too high VT. The same was true for female patients who were much more prone to receive tidal volumes of more than 8ml/kg PBW (odds ratio of 12.15). These two results are also demonstrated by a recent observational study (16). Practically, we should take particular attention to correctly set the tidal volumes when selecting the ventilator settings in these specific patients' subgroups. To be sure to apply the correct VT, it is mandatory to obtain the patient's height to be able to compute the PBW and to take this information into account to set the ventilator. Again, even if there were some patients who received VT of more than 8 Ml/kg PBW, overall the median delivered VT were in the recommended range in our patient population.

When we considered the groups predefined as protective and non-protective VT groups, it is interesting to observe that very few patients were classified in the non protective VT group. We found no differences in outcomes (ventilation duration, ICU and hospital stay duration) between the protective and non-protective VT groups. This could however be explained by the fact that no patients received very high tidal volumes in our population.

Set PEEP values were relatively low, probably because the majority of the patients were not severely hypoxemic in the postoperative period. PEEP settings used are thus overall in line with the recommendations (17) and extreme PEEP values were never prescribed (range between 3 and 15 cmH_2O). Interestingly, set PEEP was lower in COPD patients compared to CF and ILD patients.

As already mentioned, VT and PEEP were overall prescribed according to the recommendations. Oppositely, the DP applied in our patients were often higher than the 15 cmH_20 threshold now often considered as the safety limit (18). High DP may be deleterious to the patients, in terms of morbidity and mortality (19,20). Indeed, 23/57 (40%) patients ventilated in VAC had DP above 15 cmH_20 during more than 75% of time (non-protective DP group). The patient's characteristics were the same in the non-protective and protective DP groups suggesting that receiving DP above 15 cmH_20 was related to other factors. Interestingly, ILD and other disease patients had much more often DP of more than 15 cmH_20 compared to CF and COPD patients. In other words, ILD and other disease patients were much more likely to be classified in the non-protective DP group with an OR of 3.92 ($p = 0.0176$). It is difficult to know why ILD and other disease patients were ventilated with higher DP than CF and COPD patients. However, a higher DP is an expression of reduced respiratory system compliance and we could hypothesize that as these patients had a higher BMI, they could have be more prone to develop lung atelectasis and that delivering higher PEEP could have been efficient to recruit, increase compliance and decrease driving pressure. In other words, we could imagine that using higher PEEP settings in these patients could have been better.

Patients classified in the non-protective DP group had a higher PGD score at day 3. In line, they were ventilated for a longer period of time and stayed longer in the ICU

compared to the patients from the protective DP group. They were also more often ventilated for more than 48h and for more than 7 days In addition, they were more likely to require tracheotomy, showing that difficult weaning of mechanical ventilation was more likely to occur in these patients.

To interpret these findings, it is however important to note that the patients classified in the non-protective DP group were more severely ill in the early post-operative period compared to the patients from the protective DP group as they had a higher SAPS II score and a higher SOFA score at day 1. Thus it is impossible based on the present results to determine whether the use of non-protective DP is the consequence or the cause of increased disease severity. To test the relationship between higher PGD score at day 3, longer mechanical ventilation duration, longer ICU stay duration and higher DP, it is mandatory to correct for the baseline post transplantation severity. This is planned as additional analysis but was not performed up to now. If a direct relationship was found between higher DP and worse outcomes this would be a strong rational to closely monitor DP and to adapt the ventilator settings (PEEP in particular) in order to keep DP values in a safe range, even if the existence of a DP safe range is still a matter of debate.

Several limitations of this study must be underlined. First, only 60 patients were included in the analysis. Second, data were collected retrospectively. Very complete data automatically recorded in the clinician information system were however available for the analysis. Third, DP was computed based on a dynamic measurement of plateau pressure which could sometimes be overestimated. Similarly, no expiratory pause was performed to compute total PEEP, which could also be responsible for an approximation of DP. Fourth, we only considered mechanical ventilation applied in the post-operative period even if it seems probable that mechanical ventilation both delivered to the donor and used in the operating room could have some influence. Fifth, we did not take into account the transplanted lung size which could be a better determinant to compute the safest tidal volume to deliver in the post-transplant period. Finally as some patients were transferred to other hospital, the total duration of hospital stay could be underestimated. As only one patient was transferred to another ICU, ICU stay duration was not influenced by transfers.

5. Conclusion

Our retrospective study showed that in the Lausanne adult ICU, lung transplant patients were overall ventilated only during a short period of time. During the period of controlled ventilation, volume assist control was the preferred mode. Set tidal volumes were in the large majority of cases within the recommended range. PEEP was set to low values but overall in accordance to patients' severity. Oppositely, DP applied was often higher than usually recommended. There was no relationship between delivered VT and ventilator or general outcomes but very few large VT were used in our patient's population. Patients ventilated with higher DP were ventilated

for a longer period of time and stayed longer in the ICU, suggesting a potential deleterious effect of high DP. Patients who received high DP were however more severely ill in the early post-operative period. To be able to definitely conclude to a potential deleterious effect of high DP, further analyses to correct for the effect of disease severity in the post-operative period must be performed.

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